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BREAST CANCER RISK ASSOCIATED WITH GYNECOLOGIC SURGERY AND INDICATIONS FOR SUCH SURGERY

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Risk of breast cancer was assessed in relationship to gynecologic operations using data from a record-linkage study involving 15,844 women in the Uppsala Health Care Region of Sweden, who underwent surgery between 1965 and 1983. Data abstracted from medical records for the breast cancer cases and a random sample of the cohort allowed examination of risk associated with these operations in regard to menopausal status and indications for the operations. Among women who were pre-menopausal at the time of operation, a bilateral oophorectomy before the age of 50 years was associated with a 50% reduction in the risk of breast cancer compared with the background population, a reduction in risk evident within 10 years of the operation. A bilateral oophorectomy after the age of 50 years in pre-menopausal women or after a natural menopause was not associated with any reduction in risk. There were no reductions in risk associated with a unilateral oophorectomy or hysterectomy among women who were pre-menopausal at the time of operation. In fact, hysterectomy alone was associated with a slight increase in breast cancer risk when the operation was due to myomas, abnormal bleeding, and, possibly, severe forms of endometriosis but not to other reasons. Risk did not vary substantially by indications for oophorectomy, including benign ovarian neoplasms and functional ovarian cysts, though endometriosis was associated with a non-significant increase in breast cancer risk. *Int. J. Cancer, 70:150–154, 1997.*

It is well recognized that women undergoing a bilateral oophorectomy at a young age experience a low risk of subsequent breast cancer, most likely due to the marked reduction in circulating levels of the ovarian hormones estrogen and progesterone following the removal of the ovaries (Brinton *et al.*, 1988; Irwin *et al.*, 1988; Hirayama and Wynder, 1962). This conclusion, however, has primarily been derived from case-control studies, and a number of issues remain unresolved. In particular, the validity of the information on the operative procedure remains questionable, particularly with regard to the number of ovaries removed. In addition, latency effects following a bilateral oophorectomy have not been resolved. Although there is some indication that it takes 10–15 years before a protective effect becomes manifest (Brinton *et al.*, 1988), it is unclear whether this time lag is dependent on other factors, such as age of the patient at surgery. Questions also remain as to whether there is any alteration in risk if either one ovary or the uterus is removed and whether indications for the operation are important determinants of risk.

In addition, the effects of ovarian ablation after menopause have not been well established. Several studies of breast cancer incidence following radiotherapy for cervical cancer or benign gynecologic disease have documented a decreased risk of breast cancer, even among women who were irradiated after the age of 50 years (Inskip, 1994). It has been hypothesized that this reduction in risk is due to radiation-induced injury to the androgen-secreting cells of the ovarian stroma in post-menopausal women, suggesting a role of continued production of androgens by the post-menopausal ovary in the etiology of breast cancer (Inskip, 1994).

To further examine the effects of gynecologic surgery and the indications for such surgery on breast cancer risk, we have used data from a population-based record-linkage study in Sweden. The study design afforded the opportunity to examine risk among women who were pre-menopausal or naturally menopausal at the time of operation.

MATERIAL AND METHODS

The study cohort included all women in the Uppsala Health Care Region of Sweden, who were identified from a computerized registry of inpatient somatic care as having undergone a hysterectomy and/or oophorectomy during the period 1965–1983. The Uppsala Health Care Region is a geographically defined administrative unit for health care. It comprises 6 counties located in the central part of Sweden, with about one-sixth of the Swedish population (National Board of Health and Welfare, 1969). All individuals living in the region who underwent somatic inpatient care were included in the registry irrespective of the hospital in Sweden in which they were treated. Coverage of admissions is 97% complete (Naessen *et al.*, 1989). The Inpatient Registry includes date of admission and numerical codes (ICD) for diagnoses and surgical procedures.

All cancers diagnosed in the cohort between 1965 and 1987 were then identified through record linkage with the Swedish National Cancer Registry (The Cancer Registry, 1984). Linkage was accomplished by means of national registration numbers, 10-digit numbers recorded on all Swedish registries which allow exclusive identification of an individual. The cohort was also linked to the National Death Registry and Population Registry through 1987 to identify women who had died or emigrated.

The final analytic cohort included 15,844 women. Women whose operation was due to a malignancy (other than skin cancer) or who had a malignancy within 3 months of the operation were excluded, as were those with a malignancy other than skin cancer prior to the operation. A total of 295 incident cases of breast cancer were identified during the follow-up period.

Because ovarian status was not available from the inpatient registry for some women who had undergone a hysterectomy, we implemented a supplementary case-cohort study in which medical records were sought for all breast cancers identified during the study period and for a random sample of the cohort (n = 1,235). The size of the sample was chosen to be approximately 4 times the sum of the cases of breast and ovarian cancer, the 2 cancers of primary interest. Results for ovarian cancer will not be presented here.

The following information was obtained from the medical records: (*i*) type of menopause (*i.e.*, pre-menopausal, natural or surgical due to either hysterectomy, hysterectomy and bilateral oophorectomy or bilateral oophorectomy alone); (*ii*) age at menopause; (*iii*) parity; (*iv*) type of operation (*i.e.*, hysterectomy alone, hysterectomy with unilateral oophorectomy, unilateral oophorec-

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tomy alone, hysterectomy with bilateral oophorectomy, bilateral oophorectomy alone, other or unknown type of operation); (*v*) age at operation; and (*vi*) the underlying conditions that led to the operation (*i.e.*, myoma, ICD-7 = 214 or ICD-8 = 218; abnormal menstruation or metrorrhagia, henceforth called "bleeding," ICD-7 = 634 and ICD-8 = 626; endometriosis, ICD-8 = 625; ovarian cyst (follicular or corpus luteal), ICD-7 = 625 and ICD-8 = 615; benign ovarian neoplasm (excluding follicular or corpus luteal cysts), ICD-7 = 216 and ICD-8 = 220; or other indication). Endometriosis was not separately identified by the ICD-7 codes and is therefore included in the category of benign neoplasms for those years. Stein-Leventhal syndrome (ICD-7 = 275.2 and ICD-8 = 256.9) was rarely diagnosed in this cohort and is included in the "other" category. Information on other breast cancer risk factors was not available. Medical records were not retrieved for 3% of women in the random sample or for 3% of the breast cancer cases.

Most of the results presented are based on the case-cohort analyses, in which the exposure experience of the random sample was used to characterize the experience of the entire cohort (J. Lubin, personal communication). Data obtained from the medical records of the sample were used to estimate the proportion of women in the analytic cohort whose operation occurred during the pre-menopausal years or resulted in menopause and the proportion whose operation occurred after a natural menopause. If menopausal status was unknown but the operation occurred before age 46 years, the woman was considered pre-menopausal at the time of the operation. Similarly, if menopausal status was unknown but the operation occurred after age 54 years, the woman was considered naturally menopausal at the time of operation. Person-years of observation in the sample were counted from 90 days after the date of the first operation until the date of diagnosis, death, emigration, date of second gynecologic operation (for women with more than one admission) or the end of the follow-up period, whichever occurred first. Expected values for each exposure group were obtained by multiplying person-years in the sample by 5-year age- and calendar year-specific incidence rates of breast cancer for the Uppsala Health Care Region. Because the sample (n = 1,235) was 7.79% of the analytic cohort (n = 15,844), the expected values derived from the sample were divided by 0.0779 to obtain an estimate of the expected values for the entire cohort. Observed cases in the cohort were then divided by the expected number of cases in the entire cohort, yielding a standardized morbidity ratio (SMR). Confidence intervals (CI) were derived, which accounted for the variability of the observed numbers of cases and the added variability in the expected values due to the sampling of the cohort (J. Lubin, personal communication).

Supplemental analyses were done using estimated rates of first breast cancer for the Uppsala Health Care Region. Rates were estimated by applying the percentage of first breast cancers in all of Sweden to the total number of breast cancers in the Uppsala Health Care Region. In fact, rates of first breast cancer from the whole of Sweden are very similar to rates of all breast cancers from the Uppsala Health Care Region. Because results based on estimated rates of first breast cancer were not meaningfully different from those based on rates of all breast cancers, only results from the latter analyses are presented. Supplemental analyses within the cohort were also conducted to avoid the problem of non-comparability of SMRs and to control for the potential confounding effect of parity. Because no significant confounding by age or parity was evident based on the internal analyses, only unadjusted SMRs from the external analyses are presented.

RESULTS

The total number of person-years accumulated in the cohort by the end of 1987 was 193,083 and the average follow-up period was 12.2 years. The median age of the women at entry to the study (*i.e.*, age at operation) was 45.7 years. Twenty-three percent of the person-years in the cohort were accumulated for ages below 45, 36% for ages 45–54, 28% for ages 55–64 and 12% for ages 65 and older. The distribution of person-years by age in the sample was nearly identical to that in the total cohort, indicating that the sample accurately reflected the experience of the cohort. The observed number of breast cancers in the cohort was 295 compared with an expected number of 275.8 based on person-years accumulated for the entire cohort. This yielded an overall SMR of 1.1 (95% CI 1.0–1.2). This result was similar to the 1.1 (95% CI 0.9–1.2) obtained by the case-cohort method, which used the person-years in the sample divided by the sampling fraction to estimate person-years for the entire cohort.

Two hundred and eight cases and 76% of the person-years occurred among women who were pre-menopausal at the time of the operation, 61 cases and 12% of the person-years occurred among those who were naturally menopausal at the time of operation and 26 cases and 12% of the person-years in the sample occurred among women whose menopausal status was uncertain or who were menopausal due to surgery prior to the study period. Among women who were pre-menopausal at the time of the operation, person-years were allocated to the following operation groups: 32% to hysterectomy alone, 19% to a hysterectomy with unilateral oophorectomy, 26% to a unilateral oophorectomy alone, 17% to a hysterectomy with a bilateral oophorectomy, 5% to a bilateral oophorectomy alone and 1% to other types of operation. The percentages of person-years among those who were naturally menopausal at the time of operation were allocated to the operation groups as follows: 4% to hysterectomy alone, 3% to hysterectomy with unilateral oophorectomy, 17% to unilateral oophorectomy alone, 32% to hysterectomy with a bilateral oophorectomy, 44% to a bilateral oophorectomy alone and 0% to other types of operation. Because there were so few women with other types of operation (2 pre-menopausal cases and no naturally menopausal cases), subjects in this category were excluded from further analyses. Subjects whose menopausal status was uncertain or whose surgical menopause occurred prior to the study period were also excluded.

The SMRs for breast cancer associated with these operation groups among women who were pre-menopausal or naturally menopausal at the time of the operation are shown in Table I. Results presented in this and all subsequent tables were derived from case-cohort analyses. There was no overall reduction in risk among women who were pre-menopausal at the time of surgery when all types of and ages at operation were considered together. Moreover, risk of breast cancer did not vary markedly according to type of surgery (without regard to age at surgery), though those who underwent a hysterectomy alone were at slightly increased risk (SMR = 1.3, 95% CI 1.0–1.6). The SMRs for unilateral oophorectomy with and without hysterectomy were similar, as were those for bilateral oophorectomy with and without hysterectomy.

Among women who were naturally menopausal at the time of surgery, there was some variation in the SMRs according to type of surgery (Table I). A bilateral oophorectomy alone was not associated with increased risk, but a bilateral oophorectomy with hysterectomy was associated with a 50% increase in risk. Similarly, the SMR associated with a unilateral oophorectomy with hysterectomy (2.2) was higher than that associated with a unilateral oophorectomy alone (1.3), though both estimates were based on small numbers of cases.

SMRs of breast cancer associated with age at operation among women who were pre-menopausal at the time of operation are shown in Table II. In view of the hypothesis that ovarian status is the most important determinant of risk, those with a bilateral oophorectomy with and without a hysterectomy were combined, as were those with a unilateral oophorectomy with and without a hysterectomy. The SMRs associated with a bilateral oophorectomy at ages 40–44 and 45–49 were 0.6 (95% CI 0.2–1.5) and 0.7 (95% CI 0.4–1.2), respectively. A bilateral oophorectomy at older ages was not associated with a reduction in risk (SMR = 1.4, 95% CI

TABLE I – SMRs[1] OF BREAST CANCER ASSOCIATED WITH SELECTED[2] GYNECOLOGIC OPERATIONS

	Premenopausal at time of operation[3]			Naturally menopausal at time of operation		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)
Operation						
Bilateral oophorectomy alone	10	9.8	1.0 (0.5–1.9)	21	23.7	0.9 (0.6–1.4)
Bilateral oophorectomy with hysterectomy	36	41.4	0.9 (0.6–1.2)	26	17.8	1.5 (1.0–2.2)
Unilateral oophorectomy alone	35	34.0	1.0 (0.7–1.4)	9	6.7	1.3 (0.7–2.7)
Unilateral oophorectomy with hysterectomy	43	39.9	1.1 (0.8–1.5)	3	1.3	2.2 (0.7–7.4)
Hysterectomy alone	82	64.8	1.3 (1.0–1.6)	2	1.8	1.1 (0.3–4.8)
Overall	206	190.0	1.1 (0.9–1.2)	61	51.3	1.2 (0.9–1.5)

[1]Derived from case-cohort analyses.–[2]Those with other or unknown types of operation or uncertain menopausal status are not included.–[3]Operation resulted in cessation of menstruation except for those who underwent unilateral oophorectomy alone.

TABLE II – SMRs[1] OF BREAST CANCER ASSOCIATED WITH AGE AT GYNECOLOGIC OPERATION AMONG WOMEN WHO WERE PREMENOPAUSAL AT TIME OF OPERATION

Age at operation (years)	Bilateral oophorectomy[2]			Unilateral oophorectomy[2]			Hysterectomy without ovarian involvement		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)
<40	0	1.2	—	20	20.4	1.0 (0.6–1.5)	14	11.3	1.2 (0.7–2.3)
40–44	4	6.9	0.6 (0.2–1.5)	29	26.1	1.1 (0.8–1.6)	32	24.6	1.3 (0.9–1.9)
45–49	17	23.9	0.7 (0.4–1.2)	22	20.8	1.1 (0.7–1.6)	27	22.8	1.2 (0.8–1.8)
≥50	25	18.5	1.4 (0.9–2.0)	7	6.6	1.1 (0.5–2.3)	9	6.2	1.5 (0.7–2.9)

[1]Derived from case-cohort analyses.–[2]Includes women with or without hysterectomy.

TABLE III – SMRs[1] OF BREAST CANCER BY TYPE OF OPERATION, AGE AT OPERATION AND YEARS SINCE OPERATION AMONG WOMEN WHO WERE PREMENOPAUSAL AT TIME OF OPERATION

Type of operation	Age at operation (years)	Years since operation			
		SMR (95% CI) (number of cases)			
		0–4	5–9	10–14	15–30
Bilateral oophorectomy	<50	0.5 (0.2–0.9) (9)		0.8 (0.5–1.5) (12)	
	≥50	1.1 (0.3–4.8) (13)		1.8 (1.0–3.3) (12)	
Unilateral oophorectomy		1.1 (0.7–1.7) (21)	0.8 (0.5–1.3) (18)	1.4 (0.9–2.1) (25)	1.0 (0.6–1.6) (14)
Hysterectomy without ovarian involvement		1.2 (0.8–1.8) (24)	1.0 (0.6–1.7) (20)	1.2 (0.7–1.9) (17)	1.9 (1.2–3.0) (21)

[1]Derived from case-cohort analyses.

0.9–2.0). Neither age at unilateral oophorectomy nor age at hysterectomy was associated with breast cancer risk.

Among women who were naturally menopausal at the time of operation, the number of cases of breast cancer was sufficient to examine age at operation only among those who underwent a bilateral oophorectomy. Among those who had a bilateral oophorectomy with hysterectomy, the SMRs for operations at ages 50–54 and 55 or older were 1.1 (95% CI 0.4–2.9) and 1.6 (95% CI 1.0–2.5), respectively. Among those who underwent a bilateral oophorectomy alone, the corresponding SMRs were 1.3 (95% CI 0.6–3.0) and 0.8 (95% CI 0.5–1.4). No cases had operations at younger ages.

SMRs of breast cancer among women who were pre-menopausal at the time of operation by years since the operation are shown in Table III. Among those with a bilateral oophorectomy before the age of 50, risk was decreased within 10 years of the operation (SMR = 0.5) and remained reduced after 10 or more years (SMR = 0.8). Among those with a bilateral oophorectomy at ages 50 or older and those with a hysterectomy without ovarian involvement, risks associated with the longest latency periods were significantly elevated (SMRs = 1.8 and 1.9, respectively). There was no trend in risk associated with years since operation among those who had undergone a unilateral oophorectomy.

In examining risk associated with indications for the operations, results are presented for the combined group of pre-menopausal and naturally menopausal women at the time of the operation as no major differences were noted when these groups were examined separately. Shown in Table IV are analyses of indications for hysterectomy among those who underwent a hysterectomy without ovarian ablation. The predominant indication for these operations was myoma (listed in 75% of the medical records), with smaller percentages due to abnormal bleeding (19%), endometriosis (11%) or other reasons (22%). Breast cancer risk associated with hysterectomy due to myomas was 30% higher than that of the background population, and that associated with hysterectomy due to bleeding was approximately 50% higher. Endometriosis as the sole indication for surgery was associated with a more than 3-fold increase in risk. Results were similar when all women with hysterectomy, except those who also underwent a bilateral oophorectomy before age 50, were included in the analysis. In this larger group, risk

TABLE IV – SMRs[1] OF BREAST CANCER BY INDICATIONS FOR OPERATION

Indications not mutually exclusive	O	E	SMR (95% CI)	Indications mutually exclusive	O	E	SMR (95% CI)
Indications in those who underwent hysterectomy without ovarian ablation							
Myoma[2]	69	54.1	1.3 (1.0–1.6)	Myoma only	53	40.1	1.3 (1.0–1.7)
Bleeding[2]	15	9.7	1.5 (0.9–2.6)	Bleeding only	7	5.0	1.4 (0.7–3.0)
Endometriosis[2]	5	6.1	0.8 (0.3–2.0)	Endometriosis only	5	1.6	3.2 (1.2–8.0)
Other reasons[2]	7	12.3	0.6 (0.3–1.2)	Other reasons only	2	3.7	0.5 (0.1–2.2)
Indications in those who underwent oophorectomy without hysterectomy[3]							
Ovarian neoplasm[2]	46	44.4	1.0 (0.8–1.4)	Ovarian neoplasm only	33	35.4	0.9 (0.7–1.3)
Ovarian cyst[2]	11	13.1	0.8 (0.5–1.5)	Ovarian cyst only	7	7.3	1.0 (0.4–2.1)
Endometriosis[2]	8	5.9	1.4 (0.7–2.8)	Endometriosis only	5	3.0	1.7 (0.7–4.1)
Other reasons[2]	16	18.6	0.9 (0.5–1.4)	Other reasons only	10	10.5	1.0 (0.5–1.8)

[1]Derived from case-cohort analyses.–[2]May also have had other indications.–[3]Among women who underwent unilateral oophorectomy without hysterectomy at any age or a bilateral oophorectomy without hysterectomy at age 50 years or older.

associated with an indication of myoma did not vary systematically by age.

Analyses of indications for oophorectomy among women who underwent a bilateral oophorectomy without hysterectomy after age 50 are also shown in Table IV. In 55% of the medical records, a benign neoplasm was listed as an indication for the operation, whereas cysts and endometriosis were listed in 21% and 13% of the medical records, respectively. Neither benign ovarian neoplasms nor cysts were associated with an increase in breast cancer risk. An indication of endometriosis alone or in the presence of other indications was associated with a slight increase in risk. Additional analyses of indications for oophorectomy were conducted among those who also underwent hysterectomy. The only notable result among these women was a significantly increased risk associated with an operation due to both a myoma and a benign neoplasm (SMR = 2.3, 95% CI 1.2–4.4).

DISCUSSION

The results of our study confirm earlier findings of a reduced risk of breast cancer in women undergoing a bilateral oophorectomy at an early age (Brinton *et al.*, 1988; Irwin *et al.*, 1988; Hirayama and Wynder, 1962; Feinleib, 1968; Trichopoulos *et al.*, 1972). Moreover, our data demonstrate a significant reduction in risk in the first 10 years following ovarian ablation, suggesting a more immediate effect of hormones than have other studies, in which a pronounced reduction in risk was not evident for at least 10 years following surgery (Brinton *et al.*, 1988; Trichopoulos *et al.*, 1972). Results similar to ours have been reported in at least one other study (Irwin *et al.*, 1988).

Our study provides no evidence that a unilateral oophorectomy in pre-menopausal women affects risk of breast cancer. Moreover, the present findings do not support earlier reports that a hysterectomy alone (Irwin *et al.*, 1988) or with the removal of one ovary (Hirayama and Wynder, 1962) has a protective effect on breast cancer risk. In this regard, our results are consistent with a number of other studies (Brinton *et al.*, 1988; Feinleib, 1968; Trichopoulos *et al.*, 1972). Our results are also supported by reports that ovarian function remains unchanged in the majority of pre-menopausal women who undergo a hysterectomy with the conservation of both ovaries (Souza *et al.*, 1986).

Our results showing no reduction in risk associated with oophorectomy after a natural menopause do not support the hypothesis that the ablation of ovarian androgen production after menopause decreases breast cancer risk. A possible explanation for the discrepancy between our results and those of studies showing a reduced risk of breast cancer in women treated with radiotherapy after the age of 50 (Inskip, 1994) is that radiation may suppress hormone production in the adrenal gland or fat tissue as well as in the ovary (Eby *et al.*, 1989).

Our finding of a slightly increased risk of breast cancer associated with uterine myomas requiring surgery is consistent with at least one other study, which found a slight increase in risk in pre-menopausal breast cancer risk among women with myomas (Lindegard, 1990). Another study, however, found no association between myomas and breast cancer risk (Hirayama and Wynder, 1962). The constellation of risk factors for myomas, including nulliparity, obesity, earlier age at menarche and a higher level of education (Parazzini *et al.*, 1988), are similar to those for breast cancer, suggesting that myomas and breast cancer may have related hormonal etiologies.

Abnormal bleeding was associated with a slight increase in breast cancer risk in this study population, similar to the results of another study (Moseson *et al.*, 1993). Chronic menometrorrhagia of unknown cause is a frequent indication for hysterectomy (Brumsted and Riddick, 1994). Anatomic abnormalities, such as myomas, are also a cause of uterine bleeding in ovulatory women, whereas anovulatory uterine bleeding is frequently associated with an endocrine disturbance, such as excessive androgen production. The most common cause of excessive androgen production in anovulatory women is polycystic ovary disease, which was rarely identified as an indication for operation in our study.

Risk of breast cancer in this study population was not substantially altered by the presence of benign ovarian neoplasms in women who did not undergo a hysterectomy or by the presence of functional ovarian cysts (follicular or corpus luteum). The increase in risk associated with benign neoplasms among women who also underwent a hysterectomy for myomas must be interpreted cautiously in view of the absence of an association with benign neoplasms in other sub-groups. Several other studies also have reported no association of breast cancer risk with ovarian cysts/neoplasms, but these studies did not distinguish between the 2 conditions (Franceschi *et al.*, 1990; Moseson *et al.*, 1993).

Endometriosis as the sole indication for surgery, which may represent a severe form of the disease, was associated with some increase in breast cancer risk in this study. In another study that examined endometriosis and breast cancer risk, an association was found in pre- but not post-menopausal women (Moseson *et al.*, 1993). One explanation for our results is that endometriosis, a possible cause of infertility, is particularly evident in nulliparous women or women who have delayed childbearing, both risk factors

for breast cancer (Nachtigall *et al.*, 1994). Another possible explanation is that treatment of endometriosis with medications such as danazol, which in itself is androgenic and results in chronic anovulation with hyperandrogenism, or progestational agents such as medroxyprogesterone could have an adverse effect on the breast.

Several methodologic issues bear upon the interpretation of our data. Contrary to most of the published reports, the type of operation used for analysis in this study was obtained from medical records rather than self-reports. Although information from the medical records was not available for the entire cohort (only for the cases and a random sample of the cohort), our results should be unbiased due to the randomness of the sample and the high retrieval rate of medical records. The accuracy of reporting of the type and extent of gynecologic surgery has been high in several studies (Brinton *et al.*, 1988; Irwin *et al.*, 1988), while in others it has been notably low (Hirayama and Wynder, 1962). Thus, it is reassuring that this source of bias has been minimized in our study.

Another consideration in interpreting our results is that the menopausal status of the background population was not known. We could infer, however, that a substantial proportion of the younger and older women in the reference population were pre- and post-menopausal, respectively. We also did not have adequate data on most other potential confounding variables, particularly exogenous menopausal hormones, extended use of which has been linked to a 30–80% increase in breast cancer risk (Brinton and Schairer, 1993). In one report, risk associated with a hysterectomy with one or two remaining ovaries was 1.0 for women who had used estrogen replacement therapy for 3 months or more and 0.8 for women who had never used replacement therapy, though the difference in risk in these subgroups was not statistically significant (Irwin *et al.*, 1988). Sales figures of estrogenic replacement drugs in Sweden rose from 3.65 defined daily doses per 1,000 women in 1973 to 11.8 daily doses in 1977, after which there was a decline to 9.3 in 1980 (Persson *et al.*, 1983). Although toward the end of the study period (1977–1980), the rates of prevalent estrogen treatment were low, being approximately 4–9% among women 45–59 years old (Persson *et al.*, 1983), a weak protective effect of unilateral oophorectomy or hysterectomy may have been missed in our study if these women were more likely to take replacement hormones than the general population. Moreover, hormone replacement therapy is generally more common in those with a bilateral oophorectomy. Thus, we may also have underestimated the protective effect in this group. Confounding by long duration of use of menopausal estrogens also may have contributed to the elevated risks we found with long durations after surgery among those with a hysterectomy with the retention of one or both ovaries and among those with a bilateral oophorectomy after the age of 50. It may also explain the slight increase in risk with increasing time since surgery among those with a bilateral oophorectomy before the age of 50.

In summary, our findings confirm previous reports of a protective effect of early ovarian ablation against breast cancer risk. Contrary to several other reports, however, the reduction in risk was evident within 10 years of surgery. We found no reduction in risk associated with removal of one ovary in premenopausal women or of both ovaries after menopause nor any associations with indications for oophorectomy, except endometriosis. A hysterectomy was not associated with any reduction in risk, though a small reduction in risk could have been offset by increases in risk associated with certain indications for this operation—namely, uterine myomas, bleeding and, possibly, severe forms of endometriosis.

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